Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1. (Original) An isolated protein comprising a first and second immunoglobulin variable domain sequence, wherein the isolated protein binds to a PAPP-A molecule, and the first and/or second immunoglobulin domain is at least 85% identical to an immunoglobulin variable domain sequence of a01, a02, a03, a04, a05, a06, b01, b03, b04, b05, c01, c02, c04, c05, c06, d02, d03, d04, d05, d06, e01, e02, e03, f01, f03, f05, f06, g01, g02, g03, g04, g05, B12, E06, or F05.

2. (Original) The protein of claim 1 wherein the first and/or second immunoglobulin variable domain sequence comprises at least one CDR of an immunoglobulin variable domain sequence of a01, a02, a03, a04, a05, a06, b01, b03, b04, b05, c01, c02, c04, c05, c06, d02, d03, d04, d05, d06, e01, e02, e03, f01, f03, f05, f06, g01, g02, g03, g04, g05, B12, E06, or F05.

3. (Original) The protein of claim 1 wherein the first and/or second immunoglobulin variable domain sequence comprises CDRs that have an amino acid sequence that differs by no more than 3 substitutions, insertions or deletions for every 10 amino acids relative to corresponding CDRs of an immunoglobulin variable domain sequence of a01, a02, a03, a04, a05, a06, b01, b03, b04, b05, c01, c02, c04, c05, c06, d02, d03, d04, d05, d06, e01, e02, e03, f01, f03, f05, f06, g01, g02, g03, g04, g05, B12, E06, or F05.

4. (Original) The protein of claim 1 wherein the first and/or second immunoglobulin variable domain sequence is at least 85% identical in the CDR regions to an immunoglobulin variable domain sequence of a01, a02, a03, a04, a05, a06, b01, b03, b04, b05, c01, c02, c04, c05, c06, d02, d03, d04, d05, d06, e01, e02, e03, f01, f03, f05, f06, g01, g02, g03, g04, g05, B12, E06, or F05.

5. (Original) The protein of claim 1, wherein the first and second immunoglobulin domain sequences are identical to respective immunoglobulin variable domain sequences of a01, a02, a03, a04, a05, a06, b01, b03, b04, b05, c01, c02, c04, c05, c06, d02, d03, d04, d05, d06, e01, e02, e03, f01, f03, f05, f06, g01, g02, g03, g04, g05, B12, E06, or F05.

6. (Original) The protein of 1 wherein the first and second immunoglobulin domain are components of separate polypeptide chains.

7. (Original) The protein of claim 1 herein the protein is labeled.

8. (Original) The protein of claim 1 that further comprises a cytotoxic agent.

9. (Original) The protein of claim 1 wherein the cytotoxic agent comprises an Fc domain.

10. (Original) The protein of claim 1 wherein the protein can inhibit a PAPP-A-mediated activity.

11. (Original) The protein of claim 1 wherein at least 70% of the CDR amino acid residues that are not identical to residues in the reference CDR sequences are identical to residues at corresponding positions in a human germline sequence.

12. (Original) The protein of claim 1 wherein at least 70% of the FR regions are identical to FR sequence from a human germline sequence.

13. (Original) An antibody that binds to PAPP-A and competes with, competitively inhibits binding, or binds to the same or an overlapping epitope as a01, a02, a03, a04, a05, a06, b01, b03, b04, b05, c01, c02, c04, c05, c06, d02, d03, d04, d05, d06, e01, e02, e03, f01, f03, f05, f06, g01, g02, g03, g04, g05, B12, E06, or F05.

14. (Original) A method of detecting PAPP-A, the method comprising:

providing the protein of claim 1; and

detecting binding of the protein to a sample.

15. (Original) A method of evaluating a subject, the method comprising:

administering the protein of claim 1 to a subject; and

detecting location of the protein within the subject.

16. (Original) A method of treating a subject, the method comprising:

identifying a subject in need of a PAPP-A binding protein;

administering a pharmaceutical composition comprising the protein of claim 1 to a subject in an amount effective to treat a disease or disorder.

17. (Original) The method of claim 16 wherein the disease or disorder is a proliferative disease.

18. (Original) The method of claim 16 wherein the disease or disorder comprises IGF-1 regulated growth.

19. (Original) The method of claim 16 wherein the subject has a glioblastoma.

20. (Original) The method of claim 16 wherein the subject has an osteosarcoma.

21. (Original) The method of claim 16 wherein the protein is administered by application during a surgical procedure.

22. (Original) The method of claim 16 wherein the protein is administered to a lumbar puncture.

23. (Original) The method of claim 16 wherein the subject has experienced a cardiovascular event within the previous 72 hours.

24. (Original) The method of claim 16 wherein the subject is at risk for restenosis or has restenosis.

25. (Original) The method of claim 16 wherein the subject has experienced an angioplasty within the previous 72 hours.

26. (Original) A method of modulating IGF activity in a subject, the method comprising:

providing a pharmaceutical composition comprising the protein of claim 1;

identifying a subject having a disease or disorder associated with aberrant IGF activity; and

administering the pharmaceutical composition to a subject in an amount effective to modulate IGF activity in the subject.

27. (Original) A method of reducing activity of PAPP-A in a subject, the method comprising:

identifying a subject having a disease or disorder associated with aberrant PAPP-A activity; and

administering a pharmaceutical composition comprising the protein of claim 1 to the subject in an amount effective to reduce PAPP-A activity in the subject.

28. (Original) A method of altering a cellular activity, the method comprising: providing the protein of claim 1 to the extracellular milieu of a cell, under conditions that enable the protein to interact with PAPP-A to thereby alter the IGF signalling in the cell.

29. (Currently Amended) An isolated protein comprising a light chain (LC) and heavy chain (HC) immunoglobulin variable domain sequences, wherein the isolated protein binds to a PAPP-A molecule, and comprises one or more of the following features, (A), (B), (C), (D), (E), or (F), wherein

(A) CDR1 of the LC variable region comprises:

R-A-S-[QR]-[DGRS]-[VI]-[RSN]-[NRHST]-[YDEWNS]-[LVY]-[AGNL] (SEQ ID NO:358);

R-A-S-Q-X1-[VI]-X2-X3-[YDEWNS]-X4 (SEQ ID NO:359), wherein X1, X2, and X3 are any amino acid, e.g., a hydrophilic amino acid and X4 is hydrophobic, e.g., aliphatic;

X1-X2-X3-X4-X5-X6-X7-X8 (SEQ ID NO:392), wherein X1 is N, Q, R, or K, X2 is hydrophilic, A, or G, X3 is aliphatic, X4 and X5 are hydrophilic, X6 is any amino acid, or aromatic or hydrophilic, and X7 is hydrophobic;

S-G-S-S-S-N-I-[GEDA]-[SRV]-[NY]-[TLFD]-V-[YT] (SEQ ID NO:360);

S-G-S-S-S-N-I-[GEDA]-[SRV]-[ANY]-[TLFD]-V-[NYT] (SEQ ID NO:389);

T-G-T-S-S-D-[IV]-G-[DGY]-Y-[NED]-Y-V-S (SEQ ID NO:361);

T-G-T-S-S-D-[IV]-G-[ADGY]-Y-[NKED]-[YF]-V-S (SEQ ID NO:387); or

X1-X2-X3-G-X4-Y-X5-X6-X7-X8 (SEQ ID NO:393), wherein X1 is T or S, X2 is D or E, X3 is aliphatic, X4 is hydrophilic or G, and X5 is hydrophilic or N, E, D, or Q;

(B) CDR2 of the LC variable region comprises:

[ADEG]-[AVDNE]-[ASTNV]-[STNQ]-[LRN]-[AQPR]-[TFSKP] (SEQ ID NO:384);

[ADENG]-[AVDNE]-[ASTRNV]-[STENQ]-[LRN]-[AQPR]-[TFSKP] (SEQ ID NO:385);

[ADE]-[AV]-[AST]-[ST]-[LR]-[AQ]-[TFSK] (SEQ ID NO:386);

[ST]-X1-X2-X3-[LRN]-[PRQ]-S (SEQ ID NO:382), wherein X1, X2, and X3 are hydrophilic;

[NST]-X1-X2-X3-[LRN]-[PRQ]-S (SEQ ID NO:388), wherein X1, X2, and X3 are hydrophilic

[ST]-[DN]-[DN]-Q-R-P-S (SEQ ID NO:362); or

G-A-S-[ST]-[LR]-[QA] (SEQ ID NO:363);

(C) CDR3 of the LC variable region comprises:

[QL]-Q-X1-X2-X3-X4-P-X5 (SEQ ID NO:364), wherein X1, X2, X3, X4, and X5 are any amino acid, or X1 is hydrophilic, A, or G, X2 is hydrophilic, X3 is hydrophilic, X4 is aromatic, T, R, or K, X5 is hydrophobic, and the sequence can optionally be followed by T;

Q-Q-Y-X1-X2-X3-P-[PLR]-T (SEQ ID NO:365), wherein X1 and X2 are any amino acid, and X3 is hydrophobic (e.g., aromatic);

[AGQSV]-[ATS]-X1-X2-X3-[STGA]-X4-[STRG]-[GPNF]-X5-V (SEQ ID NO:381), wherein X2, X3, and X4 are any amino acid, and X1 is aromatic, or X2 is E, D, R, T, or S, X3 is D, N, Q, K, R, or S, and X4 is S, L, T, or N;

A-W-D-D-S-L-S-G-X1-V (SEQ ID NO:366), wherein X1 is hydrophobic;

A-W-D-D-S-L-S-G-[VW]-V (SEQ ID NO:367);

A-[AT]-W-D-[DNEQ]-[ST]-L-X1-G-X2-V (SEQ ID NO:391), wherein X1 is any amino acid (e.g., S, R, T, H, N) and X2 is any amino acid, e.g., hydrophobic, e.g., V, Y, or W; or

A-[AT]-W-D-[DNEQ]-[ST]-L-[SRT]-G-[VW]-V (SEQ ID NO:368);

(D) CDR1 of the HC variable region comprises:

Y-X1-M-X2 (SEQ ID NO:369), wherein X1 and X2 are any amino acid, or X1 is W, D, K, T, R, H, or P, and X2 is N, W, D, E, P, T, R, S, V, or F;

X1-Y-X2-M-X3 (SEQ ID NO:370), wherein X1 is aromatic, X2 is any amino acid, and X3 is N, W, D, E, P, T, R, S, V, or F;

W-Y-X1-M (SEQ ID NO:371), wherein X1 is any amino acid, or X1 is W, H, or T; or

Q-Y-X1-M (SEQ ID NO:372), wherein X1 is any amino acid;

(E) CDR2 of the HC variable region comprises

I-X1-[PS]-S-G-G (SEQ ID NO:373), wherein X1 is any amino acid, hydrophobic or V, Y, W, R, S, or G;

I-X1-[PS]-S-G-G-X2-T (SEQ ID NO:374), wherein X1 and X2 are any amino acid;

I-X1-[PS]-S-G-G-X2-T (SEQ ID NO:375), wherein X1 is S, V, Y, W, R, or G, and X2 is G, K, L, R, H, F, Y, T, G, Q, D, M, I, or N; or

I-X1-[PS]-S-G-G-X2-T-X3-Y-A-D-S-V-K-G (SEQ ID NO:376), wherein X1 is S, V, Y, W, R, or G, and X2 and X3 are any amino acid; or

(F) CDR3 of the HC variable region comprises:

D-F-G-S (SEQ ID NO:394);

at least two, three, or four consecutive tyrosines;

[SG]-[SG]-W-Y (SEQ ID NO:377);

S-S-[SG]-W-Y (SEQ ID NO:378);

S-S-[SG]-W-[SY] (SEQ ID NO:383)

[RHWY]-Y-Y-Y-G-M (SEQ ID NO:379); or

[YSG]- [RHWY]-Y-Y-Y-G-M-D (SEQ ID NO:380).

30. (Original) A protein comprising a first and second immunoglobulin variable domain sequences, wherein the first immunoglobulin variable domain sequence comprises the light chain variable domain of B12 and the second immunoglobulin variable domain sequence comprises the heavy chain variable domain of B12.

31. (Original) A protein comprising a first and second immunoglobulin variable domain sequences, wherein the first immunoglobulin variable domain sequence comprises the light chain variable domain of F05and the second immunoglobulin variable domain comprises the heavy chain variable domain of F05.

32. (Original) A nucleic acid comprising a sequence encoding at least one variable domain of the protein of claim 1 or a nucleic acid that hybridizes under stringent conditions to such a coding sequence.

33. (Original) A nucleic acid comprising a sequence encoding at least one variable domain of the protein of claim 1 or a nucleic acid that (i) hybridizes under stringent conditions to a sequence encoding at least one variable domain of the protein of claim 1, and (ii) encodes an immunoglobulin variable domain.

34. (Original) A host cell comprising a nucleic acid comprising a sequence encoding at least one variable domain of the protein of claim 1, operably linked to a promoter.

35. (Original) A host cell comprising a nucleic acid comprising a coding sequence that (i) hybridizes under stringent conditions to a sequence encoding at least one variable domain of the protein of claim 1, and (ii) encodes an immunoglobulin variable domain, wherein the sequence is operably linked to a promoter.

36. (Original) A host cell comprising a nucleic acid comprising a first coding sequence that encodes a light chain of a PAPP-A binding antibody, and a second coding sequence that encodes a heavy chain of the antibody, wherein the antibody is selected from the group consisting of a01, a02, a03, a04, a05, a06, b01, b03, b04, b05, c01, c02, c04, c05, c06, d02, d03, d04, d05, d06, e01, e02, e03, f01, f03, f05, f06, g01, g02, g03, g04, g05, B12, E06, and F05.

37. (Original) The host cell of claim 36 wherein the antibody is a full length IgG.